RATIONAL SUSCEPTIBILITY TEST INTERPRETIVE CRITERIA

Perspectives from the USCAST

Paul G. Ambrose, Pharm.D, FIDSA

Chair, USCAST Executive Committee

LECTURE OUTLINE
Where We're Going Today

- Introduction to USCAST
- Review of PK-PD first principles
  - Goal: Describe the types of questions answered by pre-clinical infection models
- Review the desirable attributes of appropriately determined susceptibility test interpretive criteria
  - Goal: Describe USCAST collective view on clinical breakpoints
- Review a case study
  - Goal: Describe the pitfalls of reliance on MIC and clinical data

USCAST
Who Are These Guys?

- EUCAST functions as the breakpoint committee of the:
  - o European Medicine Agency (EMA) and
  - o Committee for Medicinal Products for Human Use (CHMP)
- EUCAST is jointly organized by:
  - o European Society of Clinical Microbiology and Infectious Disease (ESCMID);
  - o European Centre for Disease Prevention and Control (ECDC); and
  - o National Breakpoint Committees (NACs)
- USCAST is the United States National Committee on Antimicrobial Susceptibility Testing (a NAC)

USCAST
Organization and Mission

- USCAST is in process as a non-for-profit 501c(3) corporation
- USCAST mission is to:
  - Provide an United States perspective on issues relating to antimicrobial resistance to EUCAST/EMA
  - Provide susceptibility test interpretive criteria recommendations to EUCAST/EMA, US FDA and other interested parties

PROMOTE INTERNATIONAL HARMONIZATION OF BREAKPOINT CRITERIA

USCAST
Executive Committee

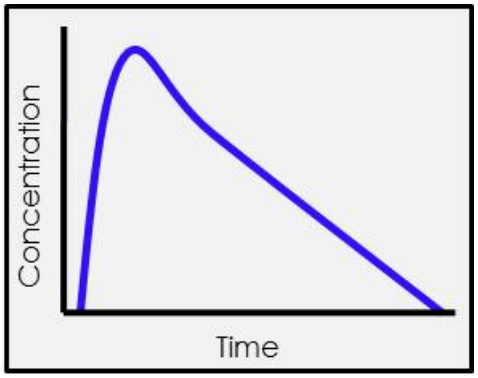
USCAST Executive Committee and Members	Society Representation
Paul G. Ambrose, Pharm.D, FIDSA *Executive Committee, Chair*	International Society for Antimicrobial Pharmacology
Ronald N. Jones, MD *Executive Committee, Scientific Secretary*	
John S. Bradley, MD *Executive Committee, Pediatric Infectious Disease Practice*	Pediatric Infectious Disease Society of America
William A. Craig, MD *Executive Committee, Infectious Disease Practice*	
Michael N. Dudley, Pharm.D. *Executive Committee, Pharmaceutical Industry*	
George L. Drusano, MD *Member, Anti-infective Pharmacology*	
Michael A, Pfaller, MD *Member, Clinical Laboratory Practice*	College of American Pathologists American Proficiency Institute
Fred C. Tenover, Ph.D. *Member, AST Diagnostics Industry*	

FIRST PRINCIPLES
Why Antibiotics Work In Vivo

- Absorption
- Distribution
- Metabolism
- Excretion

Dose → **Pharmacokinetics** → **Pharmacodynamics** → **Effect**

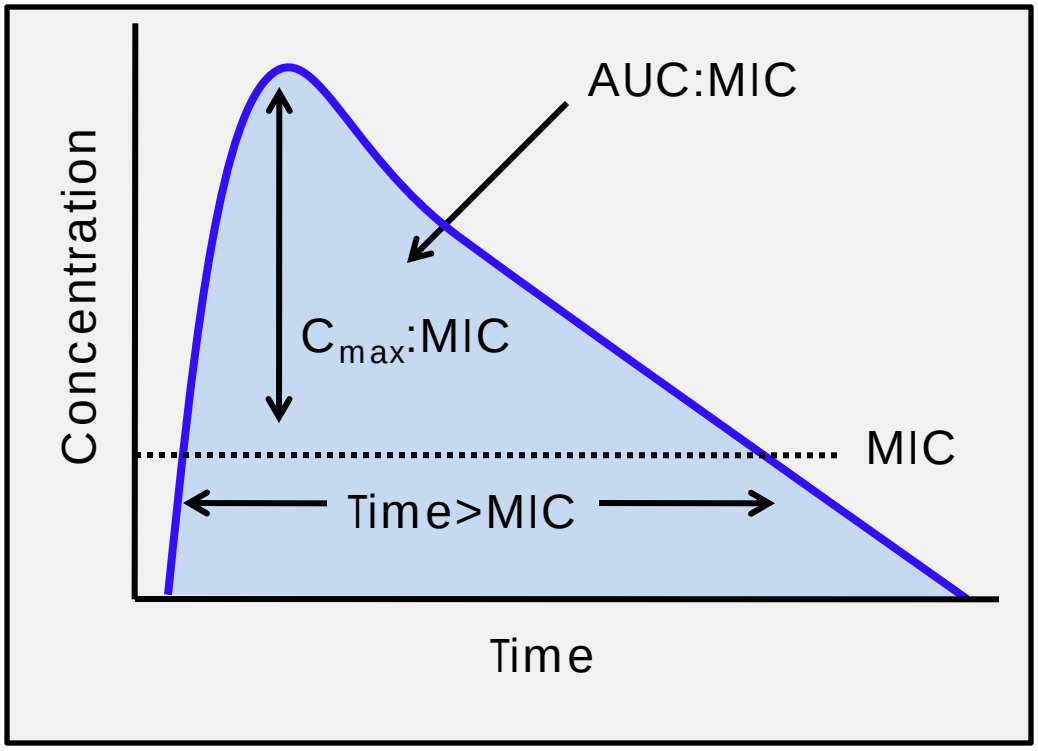
- S&S Resolution
- Mortality
- Change in CFU

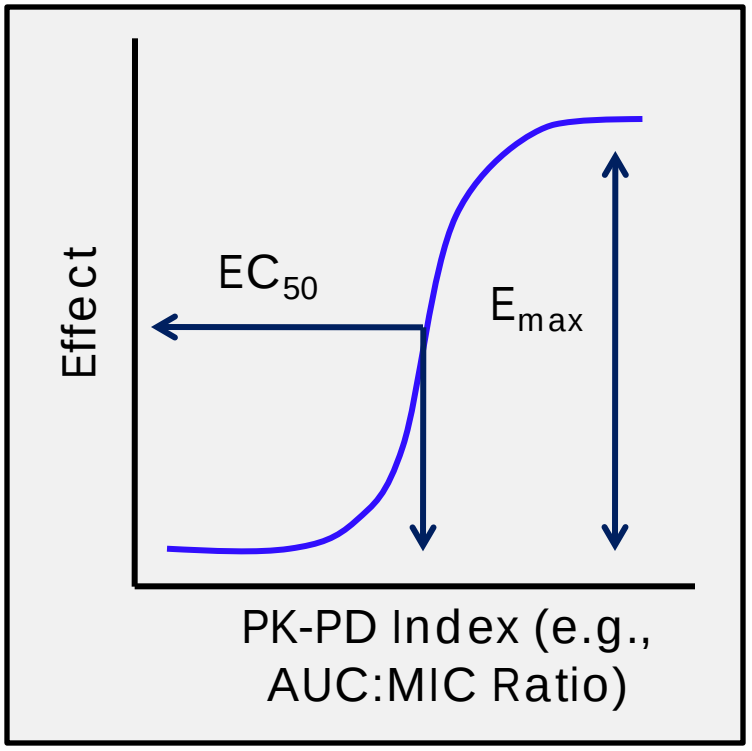


- Time-dependent killing
- Concentration-dependent killing
- Post antibiotic effects
- PK-PD indices

MN Dudley, Griffith D. *In:* Nightingale CH, Murakawa T, Ambrose PG ed. Antimicrobial Pharmacodynamics in Theory and Practice. New York, Marcel Dekker Publishers, 2002.

FIRST PRINCIPLES
Why Antibiotics Work In Vivo

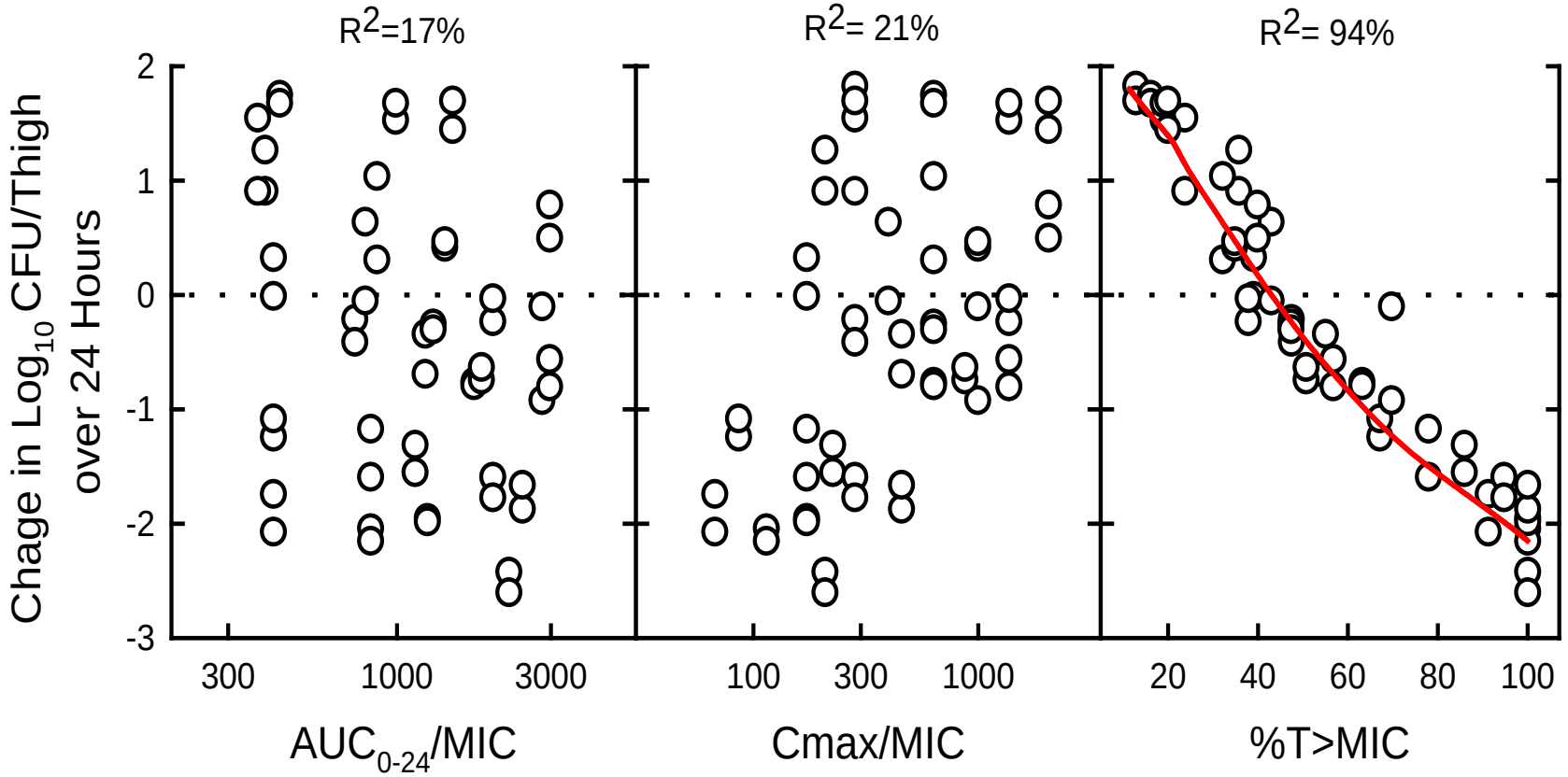




The response *in vivo* to major classes of antibacterial agents can be mapped to a relationship between pharmacokinetics and the MIC

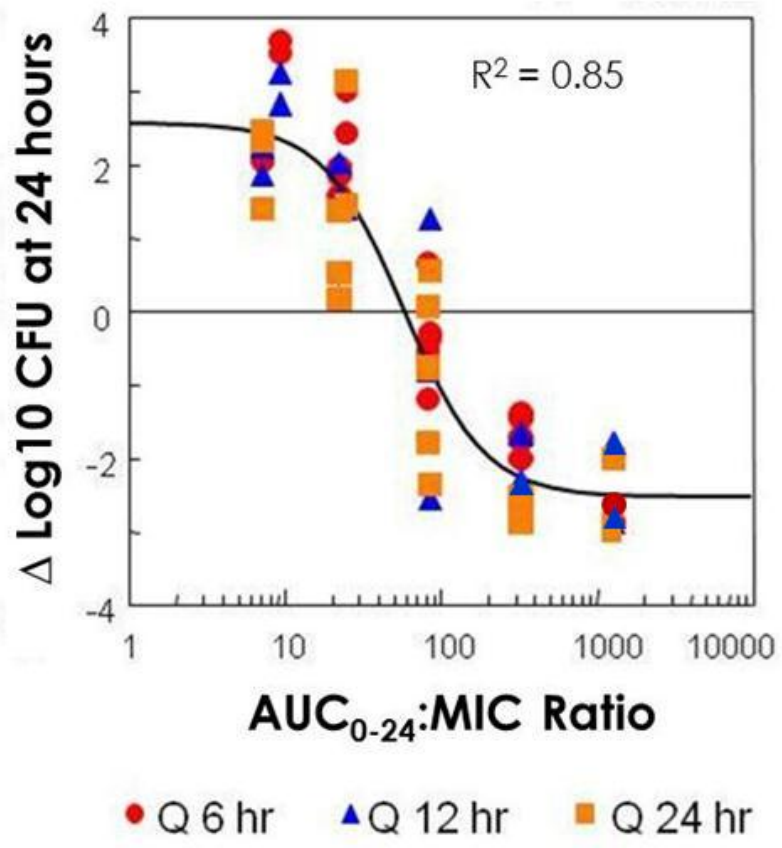
MN Dudley, Griffith D. *In:* Nightingale CH, Murakawa T, Ambrose PG ed. Antimicrobial Pharmacodynamics in Theory and Practice. New York, Marcel Dekker Publishers, 2002.

EXPOSURE & RESPONSE IN VIVO
Ceftazidime Against P. aeruginosa



Craig W Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect Dis Clin N Am 2003;17:479-501.

EXPOSURE & RESPONSE IN VIVO
Amikacin Against Gram-Negative Bacilli

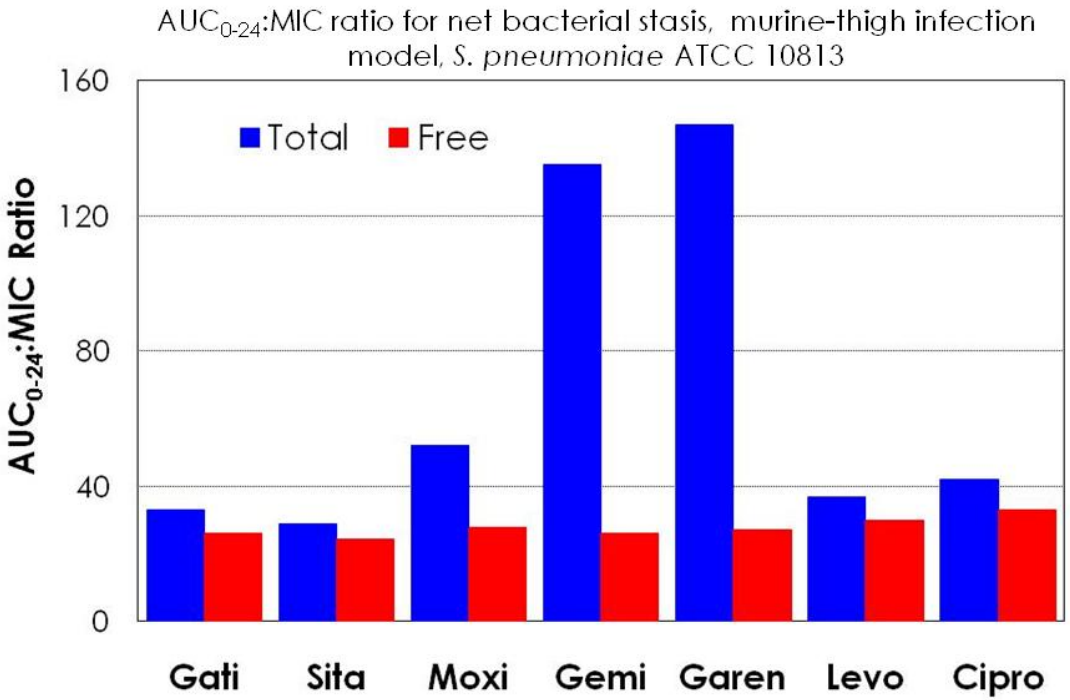


Key Question: Does the magnitude of the PK-PD measure vary with dosing interval?

The Answer: No. A given drug exposure results in same level of efficacy no matter how it is delivered

Craig WA, Andes DR, Bhavnani SM, Drusano GL, Ambrose PG. Pharmacokinetics-pharmacodynamics of amikacin against gram-negative Bacilli in a murine-thigh infection model and examination of the PK-PD variance in humans. 44th Annual Meeting of the Infectious Diseases Society of America, Toronto, Canada, October 12-15, 2006.

EXPOSURE & RESPONSE IN VIVO
Quinolones Against S. pneumoniae



Key Question: Does the magnitude of the PK-PD measure vary with protein binding?

The Answer: No. When expressed as free-drug, drug exposure results in same level of efficacy

Andes DR and Craig WA. 40th and 41st ICAAC, 2000 and 2001

EXPOSURE & RESPONSE IN VIVO

β-Lactams PK-PD Thresholds

Key Question: Does the magnitude of the PK-PD measure vary with different organisms?

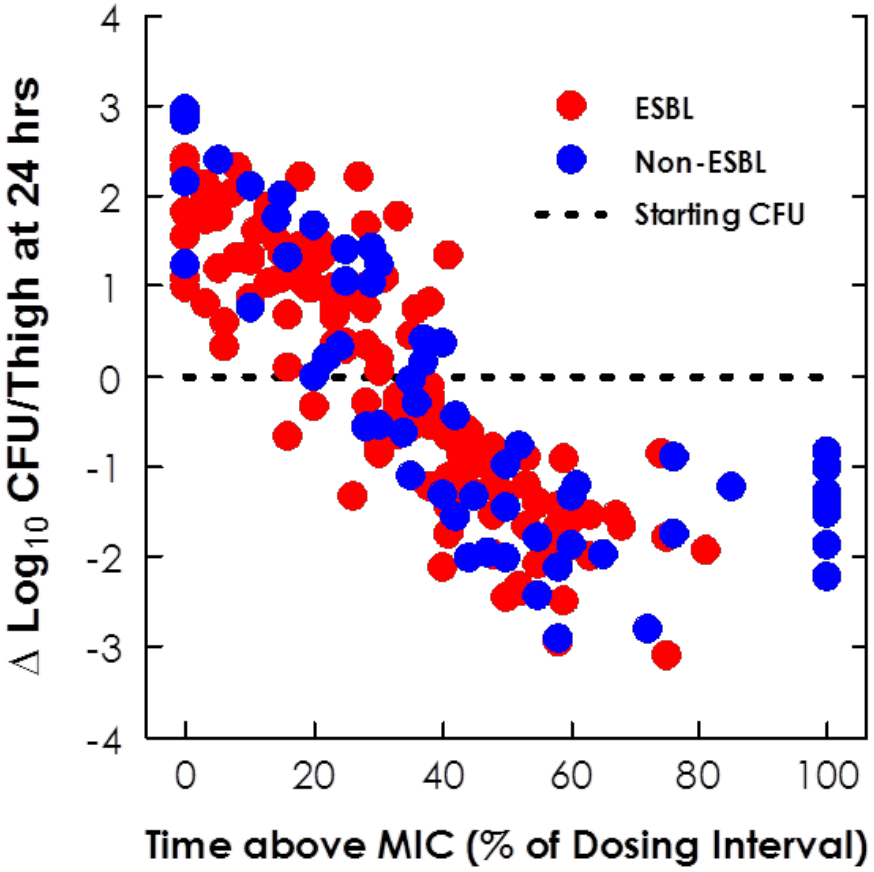
Class	Organism	Stasis	Maximum Kill
Penicillin	Gram-negative	30-40	60-70
	Pneumococci	25-35	35-50
	Staphylococci	20-30	40-50
Cephalosporin	Gram-negative	40-50	70-80
	Pneumococci	35-40	40-50
	Staphylococci	20-30	40-50
Carbapenem	Gram-negative	20-30	40-50
	Pneumococci	15-25	30-45
	Staphylococci	10-20	25-40

The Answer: Yes. Generally Gram-negative bacilli requires greater exposure than Gram-positive organisms

Data by WA Craig, yet another slide shamelessly stolen by PG Ambrose

EXPOSURE & RESPONSE IN VIVO

Cephalospornins Against Enterobacteriaceae



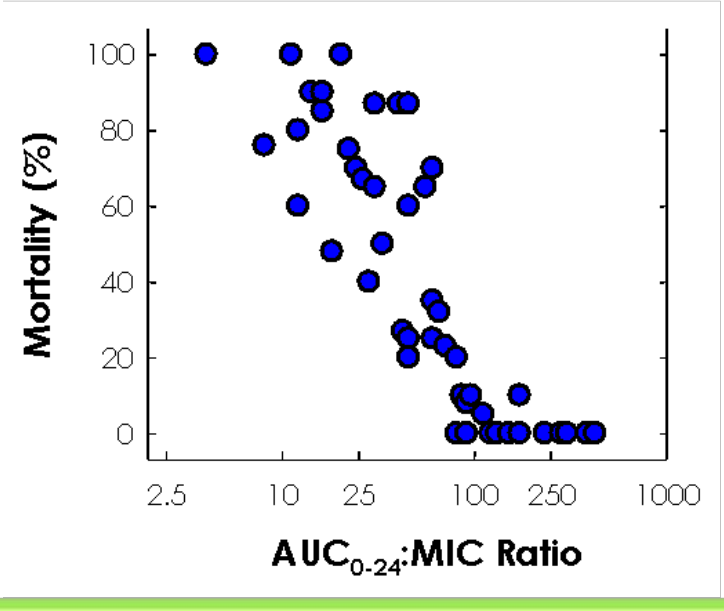
Key Question: What drives response? Is it the reason an MIC is elevated or drug exposure indexed to MIC?

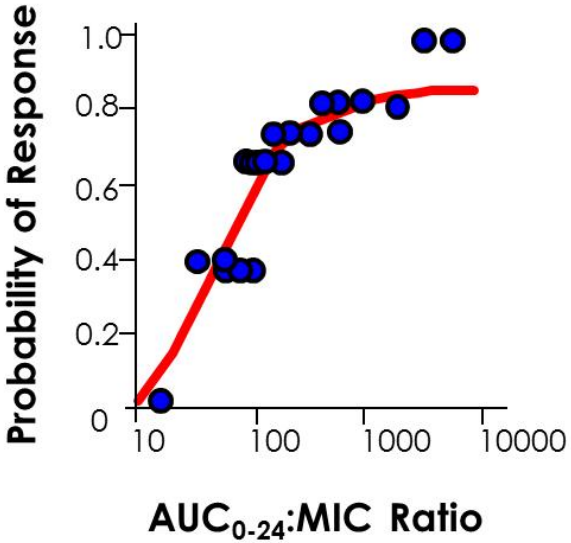
The Answer: It is not the presence or absence of particular resistance determinants that predicts outcome, but rather the drug exposure indexed to MIC

Craig WA and Andes DR. Treatment of infections with ESBL-producing organisms: pharmacokinetic-pharmacodynamic considerations. Clin Microbiol Infect. 2005;11:10-17.

EXPOSURE & RESPONSE IN VIVO
Quinolones Against Gram-Negative Bacilli

Key Question: Are the results observed in animal PK-PD infection models consistent with that in humans?



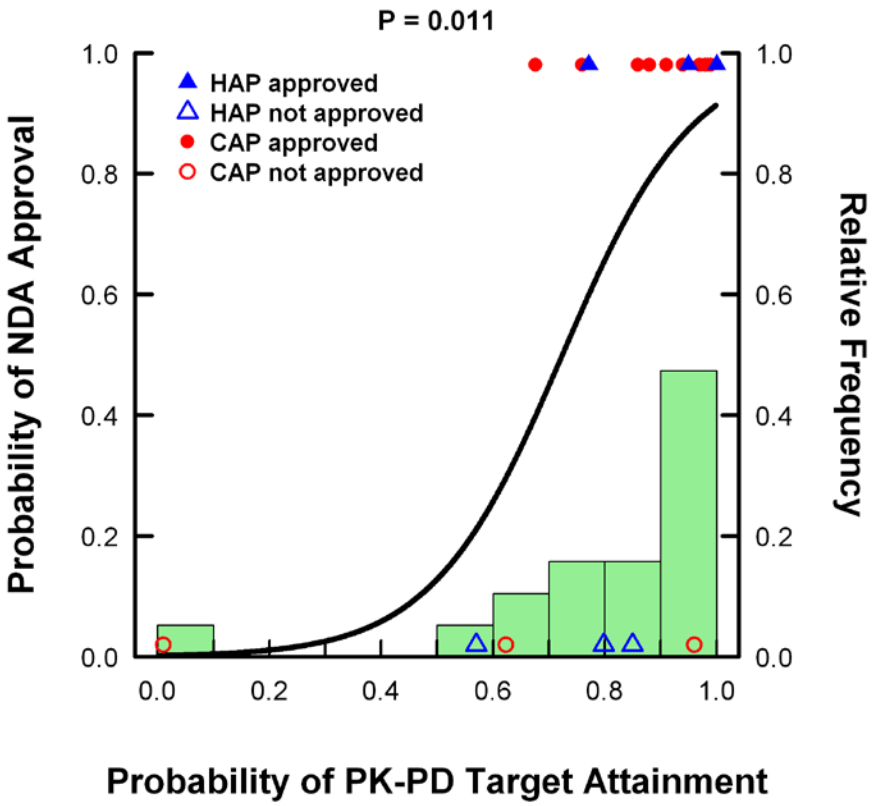


The Answer: Yes. There is good concordance across drug classes and clinical indications

Craig WA. Pharmacodynamics of Antimicrobials: General Concepts and Applications. *In:* Nightingale CH, Murakawa T, Ambrose PG ed. Antimicrobial Pharmacodynamics in Theory and Practice. New York, Marcel Dekker Publishers, 2002.

Forrest A, Nix SE, Ballow CH, Schentag, JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother.1993. 37:1073–1081

PK-PD INFECTION MODELS
Do They Forecast Regulatory Approval?



- Relationship between the regulatory approval and the probability of pre-clinical PK-PD target attainment (1996-2011)[1]
- Indications included community- and hospital-acquired pneumonia
  - 17 antibiotics in total, with 14 regulatory approvals and 6 failures

Bulik CC, Bhavnani SM, Hammel JP, Forrest A, Dudley MN, Ellis-Grosse EJ, Drusano GL, Ambrose PG. Evaluation of the Probability of Regulatory Approval Based on Pre-Clinical PK-PD Target Attainment For Community-Acquired and Hospital-Acquired Pneumonia. A-295. 53rd InterScience Conference on Antimicrobial Agents and Chemotherapy. September 10-13, 2013, Denver CO.

SUSCEPTIBILITY TEST INTERPRETIVE CRITERIA
What Should they Be?

- At a minimum, predictive of clinical response
  - If susceptibility breakpoints do not discriminate differing probabilities of response, they have little value
- Data driven by both totality and information content
  - **Least informative:** MIC and clinical outcome statistics;
    - Datasets too small , especially at the upper margin of the MIC distribution
  - **More informative:** Pharmacometric analyses of appropriate pre-clinical infection model data; and
  - **Most informative:** Multivariable pharmacometric analyses of clinical data
- Durable
  - If susceptibility breakpoints are optimally set, the need for future revision will be minimized

A CASE STUDY
Reflecting on Experience

- The goal of presenting this case study is not to gainsay our pharmaceutical company colleagues or drug regulators or…me
  - I was deeply involved in this particular development program
- The goal is to inform today's discussion

"Experience is simply the name we give our mistakes" — Oscar Wilde

TIGECYCLINE CASE STUDY
Enterobacteriaceae Breakpoints

- In 2005, tigecycline was FDA-approved for the treatment of:
  - Complicated skin and skin-structure infections and
  - Complicated intra-abdominal infections (cIAI)
- For Enterobacteriaceae, tigecycline received susceptibility test interpretive criteria of:
  - Susceptible ≤ 2 µg/mL;
  - Intermediate 4 µg/mL; and
  - Resistant ≥ 8 µg/mL

TIGECYCLINE
What have we Learned Since its Initial Approval?

- Case-reports and –series of failure and resistance-emergence on therapy appear for Gram-negative bacilli[1]
  - Majority of these isolates have initial MIC values within a dilution step of susceptible breakpoint (2 mg/L)
  - It is worth noting that there were cases of tigecycline resistance emergence on therapy associated with clinical failure during the Phase 3 cIAI program[2]
- Halted clinical trial programs
  - Hospital-acquired pneumonia[3]
  - Diabetic foot infection[4]

1: Anthony KB, Fishman NO, Linkin DR, Gasink LB, Edelstein PH, Lautenbach E. Clinical and microbiological outcomes of serious infections with multidrug–resistant gram-negative organisms treated with tigecycline. *Clin Infect Dis*. 2008;46:567-70.

2: Stein GE, Craig WA. Tigecycline: a critical analysis. *Clin Infect Dis.* 2006;43:518-24.

3: Freire AT, Melnyk V, *et al*. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. *Diagn Microbiol Infect Dis*. 2010; 68:140-51.

4: Sabol MB, Cooper A, Castaing N, *et al.* Phase 3 study comparing tigecycline and ertapenem in patients with diabetic foot infections with and without osteomyelitis. *Abstracts of the 47th Annual Meeting of the IDSA, 2009. Abstract LB-42.*

TIGECYCLINE
What have we Learned Since its Initial Approval?

- Change in the FDA Prescribing Information:

  WARNING: *"An increase in all-cause mortality has been observed across Phase 3 and 4 clinical trials in TYGACIL-treated patients versus comparator-treated patients"*[1]

  - "In general, the deaths resulted from worsening infections, complications of infection, or other underlying medical conditions" [2]

- Dosed too low or breakpoints too high—Take your pick!
  - Most analyses of mortality risk do not account for the most influential determinant of efficacy—drug exposure
  - Underscores the need for clear dose regimen justification, including PK-PD rationale for breakpoints

1: TYGACIL® (tigecycline) FOR INJECTION prescribing information. July 2010.

2: TYGACIL® (tigecycline): Drug Safety Communication-Increased Risk of Death. USFDA.gov . September 2013

TIGECYCLINE & ENTEROBACTERIACEAE
Clinical Data Basis of Breakpoints

- As I am not an FDA-employee and I was not involved in the decision, I cannot say with 100% certainty
  - However, it is not too difficult to surmise
- Enterobacteriaceae, principally *Escherichia coli*, are the most common pathogen group associated with complicated intra-abdominal infections
  - Enterobacteriaceae were isolated in 413 of 512 (80.7%) patients enrolled in the cIAI Phase 2/3 program[1], while only
  - 29of 279(10.3 %) of patients in the cSSSI Phase 3 program[2]
- Therefore, outcome by MIC likely in the cIAI program likely played a pivotal role

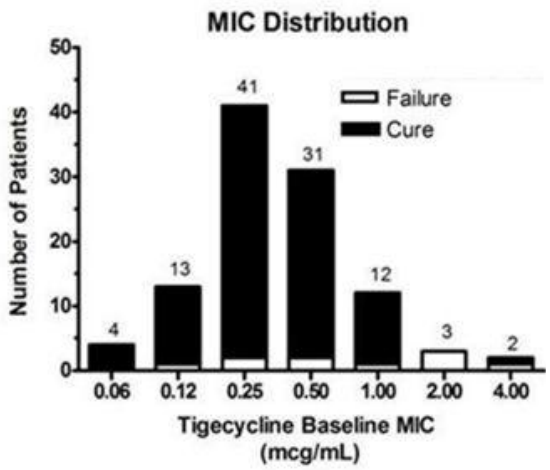
1: Babinchak T, Ellis-Grosse EJ, Dartois N, *et al*. The efficacy and safety of tigecycline in the treatment of cIAI. *Clin Infect Dis*. 2005;41:S354-66.

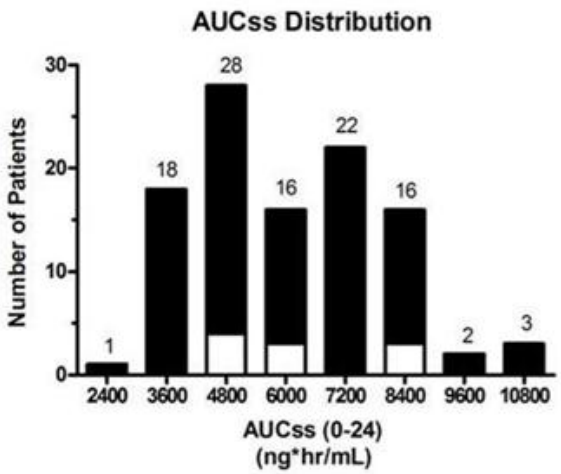
2: Ellis-Grosse EJ, Babinchak T, Dartois N, *et al*. The efficacy and safety of tigecycline in the treatment of cSSSI. *Clin Infect Dis*. 2005;41:S341-53.

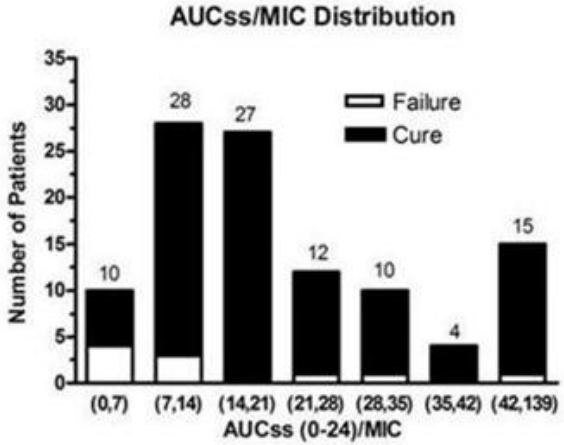
SO, NOW THE BIG QUESTION

Does Outcome by MIC Discriminate Response?

Response by the MIC, $AUC_{0–24}$ and $AUC_{0–24}$:MIC for 106 pathogens from 71 tigecycline-treated patients with complicated intra-abdominal infections[1]







Univariate evaluations of outcome by MIC value are seldom easily interpretable nor robust enough to identify predictable interpretive criteria

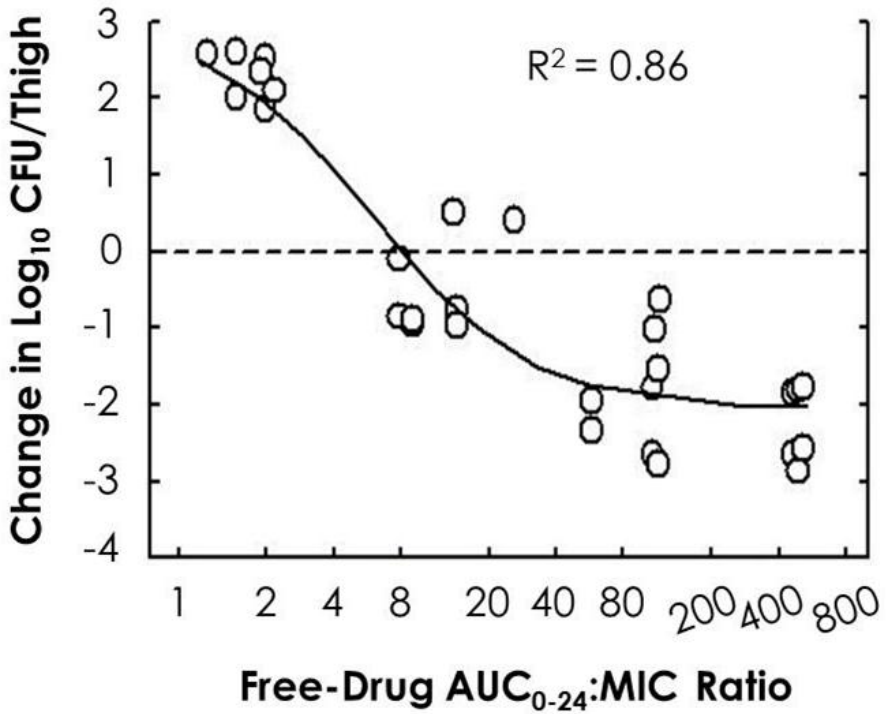
1: Ambrose PG, Bhavnani SM, Ellis-Grosse E, Drusano GL. PK-PD considerations in the design of hospital-acquired and ventilator-associated pneumonia: look before you leap! *Clin Infect Dis*. 2010;51(S1):103-110.

ANALYSES OF OUTCOME BY MIC
Take Home Message

- Clinical datasets are often too small, especially at the upper margin of the MIC distribution
  - A breakpoint set too high exposes patients to an increased risk of treatment failure
  - A breakpoint set too low denies patients an antibiotic developed to treat bacteria with elevated MIC values
- Univariate evaluations of outcome by MIC value have a high probability of a type-2 error
- For an antibiotic, indexing drug exposure to MIC provides the best opportunity to discriminate a relationship between drug exposure and effect

EXPOSURE-RESPONSE IN MICE

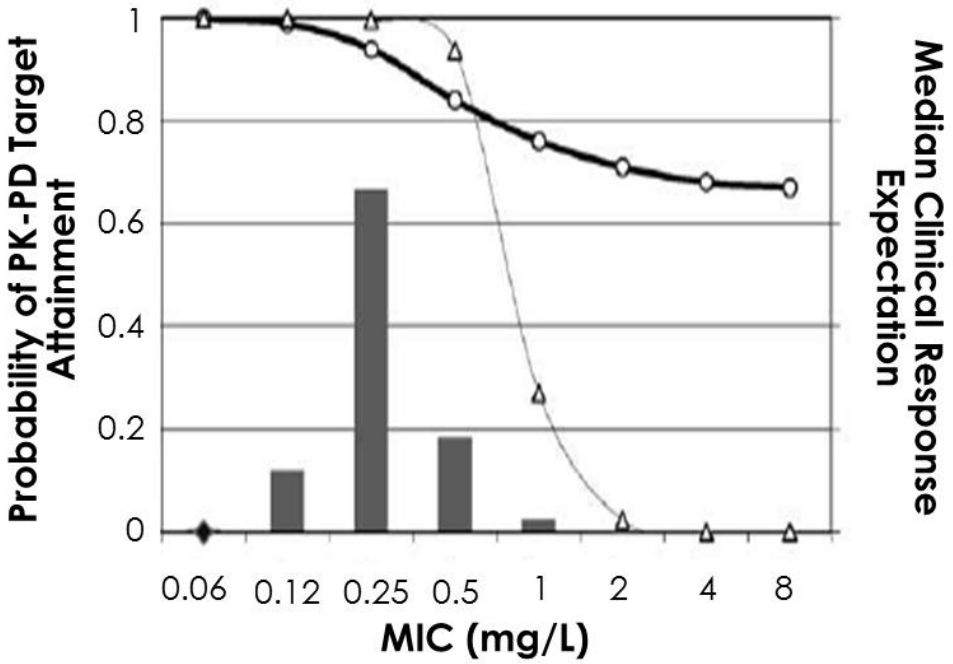
PK-PD Models Suggested Lower Breakpoints



- Tigecycline studied in a neutropenic murine-thigh infection model[1]
- *E. coli* (2) and *K. pneumoniae* (1)
- The Free-drug $AUC_{0\text{-}24}$:MIC ratio associated with net bacterial stasis, 1- and 2-$\log_{10}$ CFU reductions were 8, 18 and 250
  - Using these data and Phase 1 PK data, Monte Carlo simulation analyses suggest a susceptible breakpoint of 0.25 mg/L

1: van Ogtrop ML, Andes D, Stamstad TJ, Conklin B, Weiss WJ, Craig WA, and Vesga O. In vivo pharmacodynamic activities of two glycylcyclines against various Gram-positive and -negative bacteria. *Antimicrob. Agents Chemother*. 2000 44:943-9.

EXPOSURE-RESPONSE IN PATIENTS
PK-PD Data Suggested Lower Breakpoints



- Two tigecycline exposure-response analyses have been conducted in cIAI[1,2]
- Each identified $AUC_{0\text{-}24}$:MIC ratio as a predictor of outcome
- Using these data and Phase 2/3 PK data, Monte Carlo simulation analyses suggest a susceptible breakpoint of 0.25-0.5 mg/L[3]

1. Passarell JA, Meagher AK, Liolios K, Cirincione BB, Van Wart SA, Babinchak T, Ellis-Grosse EJ, Ambrose PG. Exposure-response analyses of tigecycline efficacy in patients with complicated intra-abdominal infections. *Antimicrob Agents Chemother* 2008; 52:204-210.
2. Bhavnani SM, Rubino CM, Ambrose PG, Babinchak TJ, Korth-Bradley JM, Drusano GL. Impact of different factors on the probability of clinical response in tigecycline-treated patients with intra-abdominal infections. Antimicrob Agents Chemother. 2010; 54:1207-1212.
3. Ambrose PG. Meagher AK, Passarell JA, Van Wart SA, Cirincinone BB, Rubino CM, Korth-Bradley JM, Ellis-Grosse. Use of a clinically-derived exposure-response relationship to evaluate potential tigecycline-Enterobacteriaceae susceptibility breakpoints. *Diagn Microbio Infect Dis.* 2009;63:38-42.

EXPOSURE-RESPONSE IN MICE AND MAN
Take Home Message

- Pre-clinical and clinical exposure-response relationships suggested similar and lower tigecycline-Enterobacteriaceae susceptibility breakpoints than those approved
- PK-PD analyses are a powerful tool, which provides a framework for evaluation of dosing regimens and in vitro susceptibility breakpoints
  - Identify breakpoints for varying dosing regimens
  - Identify breakpoints for different clinical indications
  - Evaluate the clinical meaning of *in vitro* resistance

QUESTIONS
Some Final Thoughts

Question A: Range of dose across indications. Do we change the dose to the highest licensed dose **OR** Do we lower the breakpoint to match the registered dose for an indication?

USCAST Position: This is akin to Sophie's choice

- Increasing the dose to the highest licensed dose exposes unnecessarily patients to increased risk of toxicity
- Lowering a breakpoint to march the lowest registered dose denies patients a potentially effective medicine

QUESTIONS
Some Final Thoughts

Question B: Can we have different breakpoints for different dosing regimens/indications?

USCAST Position: Yes. This option has a basis in clinical pharmacology and the decisions can be guided by PK-PD analyses

- Decreases the probability that some patients will be unnecessarily exposed to toxicity risks
- Decreases the probability that some patients will exposed to the risk associated with a suboptimal dosing regimens

THANK YOU FOR YOUR ATTENTION

Questions, Comments or Wise Remarks?

USCAST THE NATIONAL ANTIMICROBIAL SUSCEPTIBILITY TESTING COMMITTEE FOR THE UNITED STATES*